



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Registrant Copy

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

January 8, 2003

MEMORANDUM

Product Name: BIFENTHRIN TECHNICAL INSECTICIDE/MITICIDE
EPA File Symbol: 70506-RI
DP Barcode: D285143
Case No: 072204
Submission: S620915
Chemical: 128825 Bifenthrin

From: Byron T. Backus, Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505C)

Byron T. Backus
1-8-2003

To: Susan Stanton/Arnold Layne, PM 03
Insecticide-Rodenticide Branch
Registration Division (7505C)

Registrant: UNITED PHOSPHORUS INC.

ACTION REQUESTED: "United Phosphorus, Inc. has submitted an application to register a new bifenthrin technical product, claiming substantial similarity to FMC's registered technical. They wish to rely on acute toxicity data for FMC's technical to fulfill all of the acute tox requirements except oral and dermal toxicity. They have submitted their own oral toxicity (MRID#456544-04) and dermal toxicity (MRID#456544-05) studies. Please determine whether the submitted studies are acceptable and whether they may rely on FMC's data for the other acute toxicity requirements (i.e., is the product substantially similar to FMC's registered technical). Copies of the labels and CSFs for the new product and cited product (EPA Reg. No. 279-3055) are included for your information and review. Note: I was unable to locate a review of the cited acutes; however, I have a very recent draft risk assessment for bifenthrin from HED which includes the acute tox profile for bifenthrin technical based on the cited studies, except the inhalation study..."

BACKGROUND: According to the copy of the proposed label received by TRB, this product [EPA File Symbol: 70506-RI: Bifenthrin Technical Insecticide/Miticide] has the following ingredient declaration:

Active Ingredient:

Bifenthrin (2-methyl[1,1'-biphenyl]-3-yl) methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate*99.4%

Inert Ingredients:.....0.6%

As part of this package, TRB has received the following two acute toxicity studies: acute oral LD50 in rats (MRID 45654404); and acute dermal LD50 in rats (MRID 45654405).

COMMENTS AND RECOMMENDATIONS:

1. The two submitted acute toxicity studies (MRIDs 45654404 and 45654405) have been reviewed and have been classified as acceptable.
2. While the dermal toxicity study (MRID 45654405) has been classified as acceptable, The report states that in one preliminary range finding study mortality (in 1/4 rats at 500 mg/kg, 1/4 at 1000 mg/kg, and 2/4 at 2000 mg/kg) was observed; this was followed by a "main study" at 700, 1260 and 2268 mg/kg. "As sufficient mortality was not observed in the main study, the dose range finding study was conducted again using the dose levels of 500, 1000 and 2000 mg/kg...and the percent mortality observed was 0, 25 and 25, respectively." This information is considered as 6(a)(2) data [refer to CFR40 §152.125], and a more detailed report (which should include how the test material was applied and differences, if any, between the protocol(s) used in the preliminary studies and the final study) should be submitted to the Agency.
3. From the summary listing of the acute toxicity profile of Bifenthrin, it is noted that a primary eye irritation study in MRID 00132522 indicates the existing (FMC) registration for technical bifenthrin is in toxicity category IV by this exposure route. Because there may be subtle physical and/or chemical differences between the two technicals, TRB recommends that, in lieu of an actual eye irritation study for the proposed United Phosphorus Bifenthrin Technical, that it be placed in toxicity category III in terms of eye irritation potential. This is consistent with the proposed labeling for this product (which includes a FIRST AID statement for eye exposure, as well as the precautionary statement: "Causes moderate eye irritation." The remainder of the precautionary labeling (addressing inhalation toxicity, dermal irritation and dermal sensitization potentials) should then be consistent with the existing labeling for FMC technical bifenthrin.

4. Based on the results of the reviewed acute toxicity studies, as well as the considerations indicated above, the following is the acute toxicity profile for EPA File Symbol 70506-RI BIFENTHRIN TECHNICAL INSECTICIDE/MITICIDE:

Acute Oral LD50	Acceptable	Tox. Cat. II (MRID 45654404)
Acute Dermal LD50	Acceptable	Tox. Cat. III (MRID 45654405)
Acute Inhalation LC50	Cited	Tox. Cat. III(?)*
Primary Eye Irritation	Cited	Tox. Cat. III**
Primary Dermal Irritation	Cited	Tox. Cat. IV
Dermal Sensitization	Cited	Negative

*Summary sheet indicates no existing inhalation toxicity studies. Label for this proposed product is consistent with toxicity category III, and this is acceptable if the FMC product is also in toxicity category III by this exposure route.

**Summary sheet indicates the FMC product is in toxicity category IV by this exposure route. As slight physical and/or chemical differences may impact on eye irritation potential, TRB recommends that, in lieu of a primary eye irritation study on the United Phosphorus Technical Bifenthrin, that it be assigned to toxicity category III by this exposure route. This is consistent with the labeling proposed for this product by United Phosphorus.

5. Based on the acute toxicity profile given above and based on the proposed label use directions, the following is the precautionary labeling for this product, as obtained from the Label Review System:

PRODUCT ID #: 070506-00018

PRODUCT NAME: BIFENTHRIN TECHNICAL INSECTICIDE/MITICIDE

PRECAUTIONARY STATEMENTS

SIGNAL WORD: WARNING

Hazards to Humans and Domestic Animals:

May be fatal if swallowed. Harmful if absorbed through skin. Harmful if inhaled. Causes moderate eye irritation. Avoid breathing dust. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

First Aid:

If swallowed:

- Call a poison control center or doctor immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to by a poison control center or doctor.
- Do not give anything to an unconscious person.

If on skin:

- Take off contaminated clothing.
- Rinse skin immediately with plenty of water for 15-20 minutes.
- Call a poison control center or doctor for treatment advice.

If inhaled:

- Move the person to fresh air.
- If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible.
- Call a poison control center or doctor for further treatment advice.

If in eyes:

- Hold eye open and rinse slowly and gently with water for 15-20 minutes.
- Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
- Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/CRM/Registrant: The proposed label should contain a "Note to Physician". The following statements are suggested types of information that may be included, if applicable: - technical information on symptomatology; - use of supportive treatments to maintain life functions; - medicine that will counteract the specific physiological effects of the pesticide; - company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Product Manager: 03
MRID No.: 45654404

Reviewer: Byron T. Backus, Ph.D.

CITATION: Tiwari, V.K. Acute Oral Toxicity Study of Bifenthrin Technical in Rats. JRF Study No. 3415. Unpublished study prepared by Department of Toxicology, Jai Research Foundation, Valvada 396108, Gujarat, India. Final Report Date: FEB-9-2002. MRID 45654404.

SUBMITTER & SPONSOR: UNITED PHOSPHORUS INC.

TEST MATERIAL: Bifenthrin Technical; (2-methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate; CAS 82657-04-3; purity 99.2%, a white powder

SPECIES: Rat, Wistar

AGE(at dosing): young adult, 9 weeks

WEIGHT (presumably fasted): Males: 204-270 g; Females: 194-235 g

SOURCE: Breeding facility, Jai Research Foundation

EXECUTIVE SUMMARY: *In an acute oral toxicity study (MRID 45654404), fasted (17+ hrs) young adult (9 week old) Wistar rats (5 males and 5 females/dose level) were orally gavaged with Bifenthrin Technical (a white powder containing 99.2% active) in peanut oil at a constant dose volume of 10 mL/kg. Doses in the main study were 0 (vehicle only), 50, 79 and 125 mg/kg.*

At 50 mg/kg 0/5M & 2/5F died; at 79 mg/kg 4/5M & 2/5F died; at 125 mg/kg 5/5M & 3/5F died. All deaths were within 24 hours of dosage. Symptoms at all dose levels included tremors and nasal discharge; other observations (at 79 mg/kg and above) included abdominal breathing, nasal irritation and piloerection. At 125 mg/kg symptoms also included tonic-clonic convulsions in all animals. Survivors were generally normal by Day 3. All survivors had weight gains from Day 0 to Day 7 and again from Day 7 to Day 14, with the exception of one 50 mg/kg female who had the same bodyweight on Day 7 and Day 14.

The rats which died showed findings which included mottling or congestion of the liver and mottling or congestion of the lungs. 13/16 rats found dead had pulmonary congestion, and it is reported that this is a common finding in dead animals with no particular pathological significance. Findings in terminally sacrificed animals were categorized as spontaneous/accidental.

Oral LD50 Males = 66.19 (95% C.L. of 54.48 to 77.90) mg/kg

Oral LD50 Females = 91.89 (95% C.L. of 26.67 to 316.63) mg/kg

Oral LD50 Combined = 74.90 (95% C.L. of 57.29 to 97.92) mg/kg

Bifenthrin technical, a white powder containing 99.2% active ingredient, is in toxicity category II in terms of oral toxicity.

Study Classification: Acceptable

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 5), and [No] Data Confidentiality (p. 2) statements were provided.

Procedure (including deviations from 870.1100): Following preliminary range-finding testing, "four groups of rats, each dose group comprising 5 males and 5 females, were randomly selected and three groups were given a single dose of bifenthrin technical at dose levels of 50, 79 and 125 mg/kg... As the test substance is insoluble in water, it was suspended in peanut oil at the required concentrations prior to dosing. The dose solution was stirred to ensure that there were no visible precipitates. Another group was administered peanut oil at a constant dose volume of 10 mL/kg...as control. A dose volume of 10 mL/kg body weight was calculated for each rat. All animals were dosed once by gavage (day 0) using a metal cannula... Animals were deprived of feed for seventeen hours and fifteen minutes prior to dosing and then three hours after dosing."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Total
0 (vehicle only)	0/5	0/5	0/10
50	0/5	2/5	2/10
79	4/5	2/5	6/10
125	5/5	3/5	8/10

Observations: All deaths were within 24 hours of dosage. Symptoms at all dose levels included tremors and nasal discharge; other observations (at 79 mg/kg and above) included abdominal breathing, nasal irritation and piloerection. At 125 mg/kg symptoms also included tonic-clonic convulsions in all animals. Survivors were generally normal by Day 3. All survivors had weight gains from Day 0 to Day 7 and again from Day 7 to Day 14, with the exception of one 50 mg/kg female who had the same bodyweight on Day 7 and Day 14.

Gross Necropsy: The rats which died showed findings which included mottling or congestion of the liver and mottling or congestion of the lungs. 13/16 rats found dead had pulmonary congestion, and it is reported that this is a common finding in dead animals with no particular pathological significance. Findings in terminally sacrificed animals were categorized as spontaneous/accidental.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200, formerly §81-2)

Product Manager: 03
MRID No.: 45654405

Reviewer: Byron T. Backus, Ph.D.

CITATION: Tiwari, V.K. Acute Dermal Toxicity Study of Bifenthrin Technical in Rats. JRF Study No. 3416. Unpublished study prepared by Department of Toxicology, Jai Research Foundation, Valvada 396108, Gujarat, India. Final Report Date: FEB-9-2002. MRID 45654405.

SUBMITTER & SPONSOR: UNITED PHOSPHORUS INC.

TEST MATERIAL: Bifenthrin Technical; (2-methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate; CAS 82657-04-3; purity 99.2%, a white powder

SPECIES: Rat, Wistar

AGE(at dosing): not stated; presumably young adult (consistent with body weight data)

WEIGHT: Males: 229-282 g; Females: 216-259 g

SOURCE: Breeding facility, Jai Research Foundation

EXECUTIVE SUMMARY: *In an acute dermal toxicity study (MRID 45654405), groups of 5M & 5F young adult Wistar rats were dermally exposed for 24 hrs (occluded exposure) to either 2000 mg/kg Bifenthrin technical (a white powder with 99.2% purity) mixed with an unspecified amount of peanut oil "to give a slurry," or to 0.2 mL of peanut oil alone.*

There were no mortalities. 9/10 of the rats exposed to bifenthrin showed symptoms (tremors) on Day 3, and two of these rats (both males) also had tremors and piloerection on Days 4-5. All rats were normal from Day 6 through Day 14. All 5 males had bodyweight gains in the period from Day 0 to Day 7, but all 5 females had weight losses during this period; 5/5 males and 4/5 females had bodyweight gains in the period from Day 7 to Day 14.

Necropsy findings (pinpoint lung hemorrhages in one male; bilateral uterine hydrometra in one female) were considered spontaneous and unrelated to exposure to bifenthrin.

The report states that in one preliminary range finding study mortality (in 1/4 rats at 500 mg/kg, 1/4 at 1000 mg/kg, and 2/4 at 2000 mg/kg) was observed; this was followed by a "main study" at 700, 1260 and 2268 mg/kg. "As sufficient mortality was not observed in the main study, the dose range finding study was conducted again using the dose levels of 500, 1000 and 2000 mg/kg...and the percent mortality observed was 0, 25 and 25, respectively." This information is considered as 6(a)(2) data, and a detailed report should be submitted to the Agency.

Dermal LD50 Males > 2000 mg/kg (0/5 died at this dose level)

Dermal LD50 Females > 2000 mg/kg (0/5 died at this dose level)

Dermal LD50 Combined > 2000 mg/kg (0/10 died at this dose level)

Bifenthrin technical, a white powder containing 99.2% active, is in toxicity category III in terms of dermal toxicity, based on the dermal LD50 > 2000 mg/kg.

Study Classification: Acceptable

COMPLIANCE: Signed and dated GLP Compliance (p. 3), Quality Assurance (p. 5), and [No] Data Confidentiality (p. 2) statements were provided.

Procedure (including deviations from 870.1200): "A dose range finding study for bifenthrin technical was performed using four (2 male and 2 female) animals per group. The per cent mortality observed were 25, 25 and 50 at the dose levels of 500, 1000 and 2000 mg/kg body weight. Based on above results, main study was conducted at the dose level of 700, 1260 and 2268 mg/kg body weight. As sufficient mortality was not observed at the main study, the dose range finding study was conducted again using the dose levels of 500, 1000 and 2000 mg/kg body weight and the per cent mortality observed was 0, 25 and 25, respectively. Therefore, the study was conducted as a limit study using 2000 mg/kg body weight."

"Depending on the result of the range finding study, two groups of rats, comprising 5 males and 5 females per group, were randomly selected...and one group was given dermal application of bifenthrin technical at the dose level of 2000 mg/kg body weight. As bifenthrin technical was insoluble in water, the measured/calculated quantity of bifenthrin technical was mixed with peanut oil, to give a slurry, for even application on the exposed part of the skin. The other group of ten animals (5 male and 5 female), which served as control, was simultaneously treated with 0.2 mL of peanut oil and maintained in similar experimental conditions. The test substance was held in contact with the skin with a porous gauze dressing (not more than 8 ply) and Medi tape 330 hypo-allergic surgical tape...throughout the 24 hour of exposure period to prevent evaporation of the test substance and to ensure that the animals did not ingest it. At the end of the exposure period, the residual test substance was removed using cotton moistened with distilled water."

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
0	0/5	0/5	0/10
2000	0/5	0/5	0/10

Observations: None of the rats showed any clinical signs from Day 0 to Day 2. 5/5 males and 4/5 females had tremors on Day 3; all but 2 males had recovered the following day. The 2 males showed tremors and piloerection on Days 4 and 5, but were normal on Day 6. All 5 males gained weight in the period from Day 0 to Day 7, while all 5 females lost weight during this same period. All males continued to gain weight in the period from Day 7 to Day 14, but one female lost weight during this period and 3 others, although gaining some weight, had still lost a few grams from their initial (Day 0) weight.

Gross Necropsy: 2000 mg/kg: 3/5 males and 4/5 females had NAD (No abnormalities detected). One male had pin-point hemorrhages (mild) of the lungs; the other male had blotched kidneys and a few pin-point hemorrhages of the lungs. One female had partial consolidation in the right cranial lobe of the lung.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D285143
2. **PC CODE:** 128825 Bifenthrin
3. **CURRENT DATE:** January 8, 2003
4. **TEST MATERIAL:** EPA File Symbol 70506-RI; Bifenthrin Technical; (2-methyl[1,1'-biphenyl]-3-yl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate; CAS 82657-04-3; purity 99.2%, a white powder

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat/ Jai Research Foundation Gujarat India/Study No. 3415/FEB-9-2002	45654404	LD ₅₀ (M) = 66.2 (54.5-77.9) mg/kg; LD ₅₀ (F) = 91.9 (26.7-316.6)mg/kg; LD ₅₀ (Combined) = 74.9 (57.3-97.9) mg/kg. Dose levels: 50, 79 & 125 mg/kg of test material in peanut oil at a constant dose volume of 10 mL/kg. Symptoms at all dose levels included tremors and nasal discharge; other observations (at 79 mg/kg and above) included abdominal breathing, nasal irritation and piloerection. At 125 mg/kg symptoms also included tonic-clonic convulsions. Survivors were generally normal by Day 3.	II	A
Acute Dermal Toxicity/rat/ Jai Research Foundation Gujarat India/Study No. 3416/FEB-9-2002.	45654405	There were no mortalities among 5M & 5F dermally exposed to 2000 mg/kg. 9/10 rats had tremors on Day 3, and 2 of these (both males) had tremors and piloerection on Days 4-5. All rats were normal Days 0-2, Days 6-15. All 5M had bodyweight gains in the period from Day 0 to Day 7, but all 5F had weight losses; 5/5 males and 4/5 females had bodyweight gains in the period from Day 7 to Day 14. Necropsy findings (pinpoint lung hemorrhages in one male; bilateral uterine hydrometra in one female) were considered spontaneous and unrelated to exposure to bifenthrin. Report states that in a preliminary range finding study 1/4 rats at 500 mg/kg, 1/4 at 1000 mg/kg, and 2/4 at 2000 mg/kg died; followed by a "main study" at 700, 1260 and 2268 mg/kg. "As sufficient mortality was not observed in the main study, the dose range finding study was conducted again using the dose levels of 500, 1000 and 2000 mg/kg... and the percent mortality observed was 0, 25 and 25, respectively."	III	A

Core Grade Key: **A** =Acceptable, **S** = Supplementary, **U** = Unacceptable, **V** = Self Validated